Maternal microbiota shapes brain and neuroendocrine development in piglets

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Wanqiong Yuan, Jing Hang, Jialin Jia, Jie Huang, Xuanqi Zheng, Huan Wang, Tong Wu, et al. 2026. Vitamin K2 ameliorates pregnancy- and lactation-associated osteopenia and postpartum depression. ***iMeta*** 5: e70180.

https://doi.org/10.1002/imt2.70180.

Background

Porcine Large-Animal Model

- Porcine Brain
- Gyrencephalic Cortex
- Translational Relevance
- Conserved Regional Transcriptomic Profiles
- Human-like Neuroanatomy

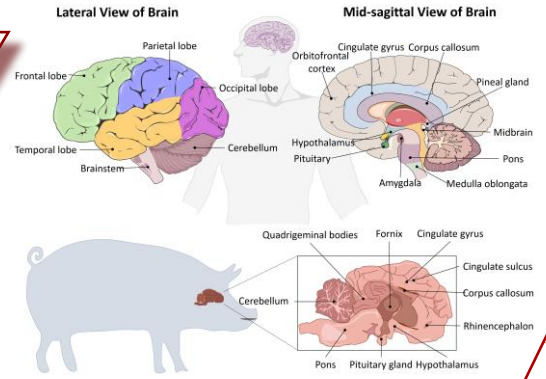
Maternal Microbiota and Early-Life Development

- Neural Development
- Glial Maturation
- Neuroendocrine Function

- Cell Composition
- Cellular and Molecular Regulation
- CellChat
- Transcriptional Regulation
- Spatial Distribution

Brain ⇄ **Gut**

Crosstalk



Known
Maternal Microbiota Shapes Early-Life Development

Unknown
Limited Cell-Resolved Mechanistic Insights in Large Mammals

Knowledge Gap
- Cross-Organ
- Cell-Resolved Evidence

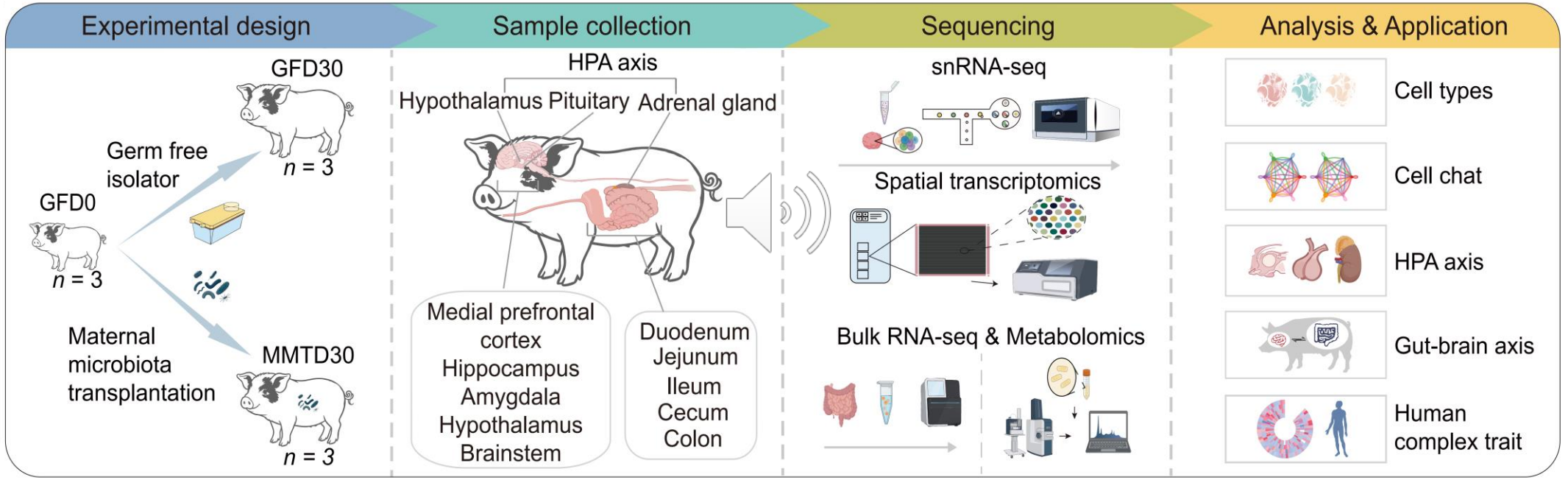
Scientific Questions
- Microbial Influence
- Regulatory Mechanisms

Research Objectives
- Cellular Atlas、Spatial Mapping
- Regulatory Networks、Multi-Omics Integration

Background

How and to what extent does maternal microbiota exposure shape early brain and neuroendocrine development?

Using germ-free piglets and maternal microbiota transplantation, this study integrates multi-organ omics across the brain, HPA axis and intestine to characterize early-life gut–brain–neuroendocrine interactions.



1. Experimental models
Germ-free piglets maternal microbiota transplantation

2. Multi-organ sampling
Five brain regions; HPA axis; Five intestinal segments

3. Multi-omics profiling
snRNA-seq; Spatial transcriptomics; bulk RNA-seq; Metabolomics

4. Integrated analyses
Cell composition; Transcriptional states; Cell–cell communication; Cross-species genetic associations

Result 1 | Maternal Microbiota-Responsive Porcine Brain Atlas

An snRNA-seq atlas comprising 504489 high-quality nuclei from five brain regions identified six major cell lineages. Compared with GFD30, MMTD30 piglets showed altered neuron, oligodendrocyte and astrocyte proportions in selected regions, together with differences in hypothalamic spatial organization.

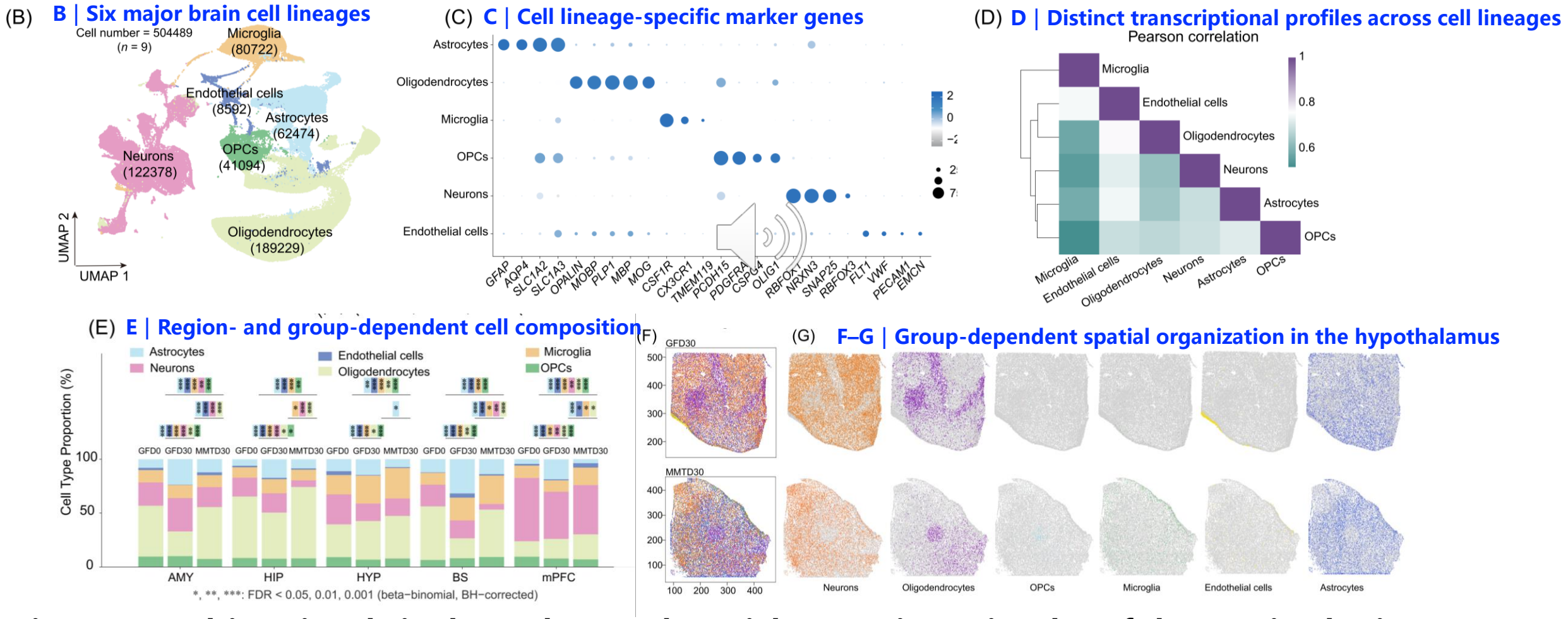


Figure 1. Multi-regional single-nucleus and spatial transcriptomic atlas of the porcine brain across developmental stages and microbial conditions.

Result 2 | Neuronal development and neuron–glia communication

Neurons exhibited prominent microbiota-associated transcriptional responses, with region- and subtype-dependent developmental signatures. CellChat predicted reorganization of neuron–glia interactions, including higher inferred NRG1/3–ERBB4 communication probabilities, accompanied by significantly increased plasma glutamic acid and glutamine.

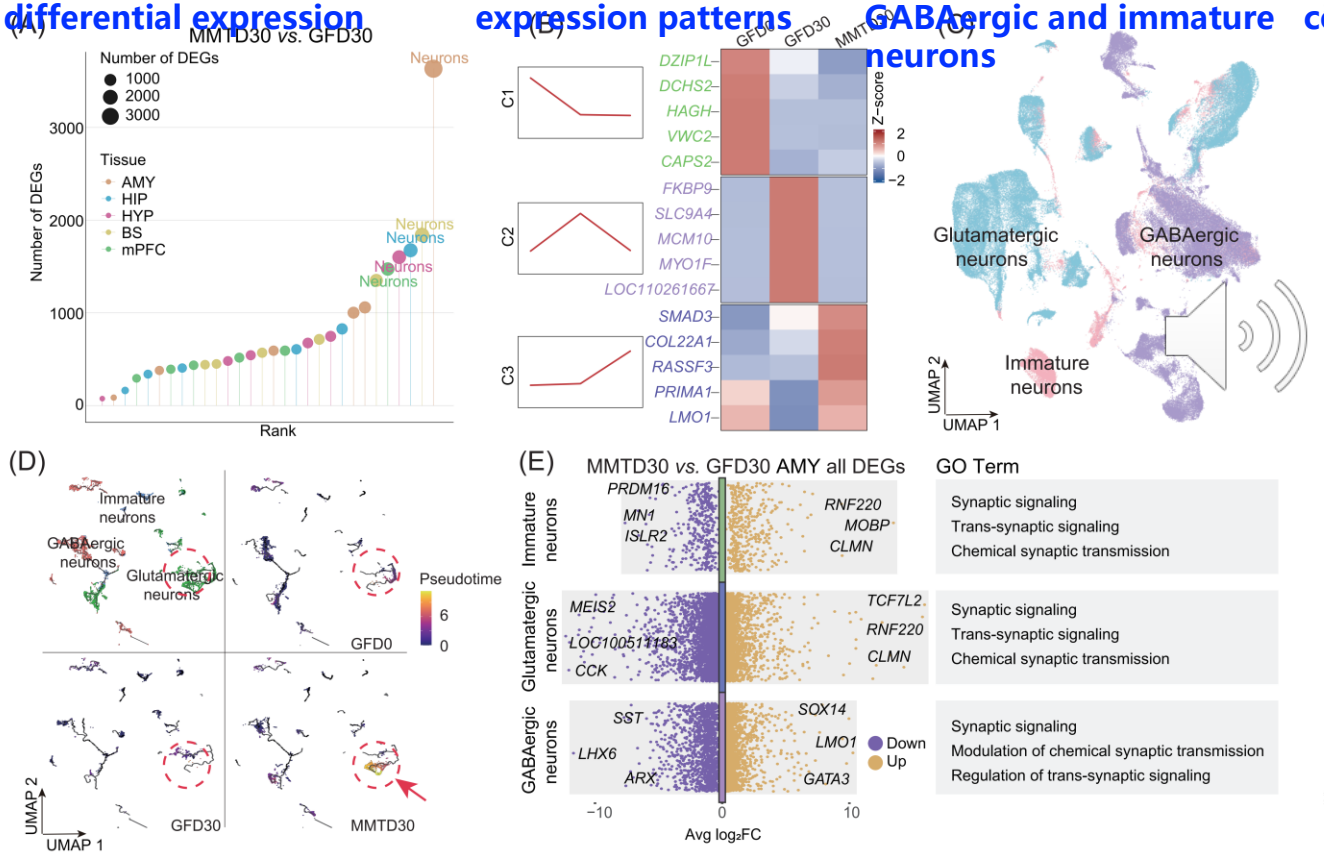
A | Prominent neuronal differential expression

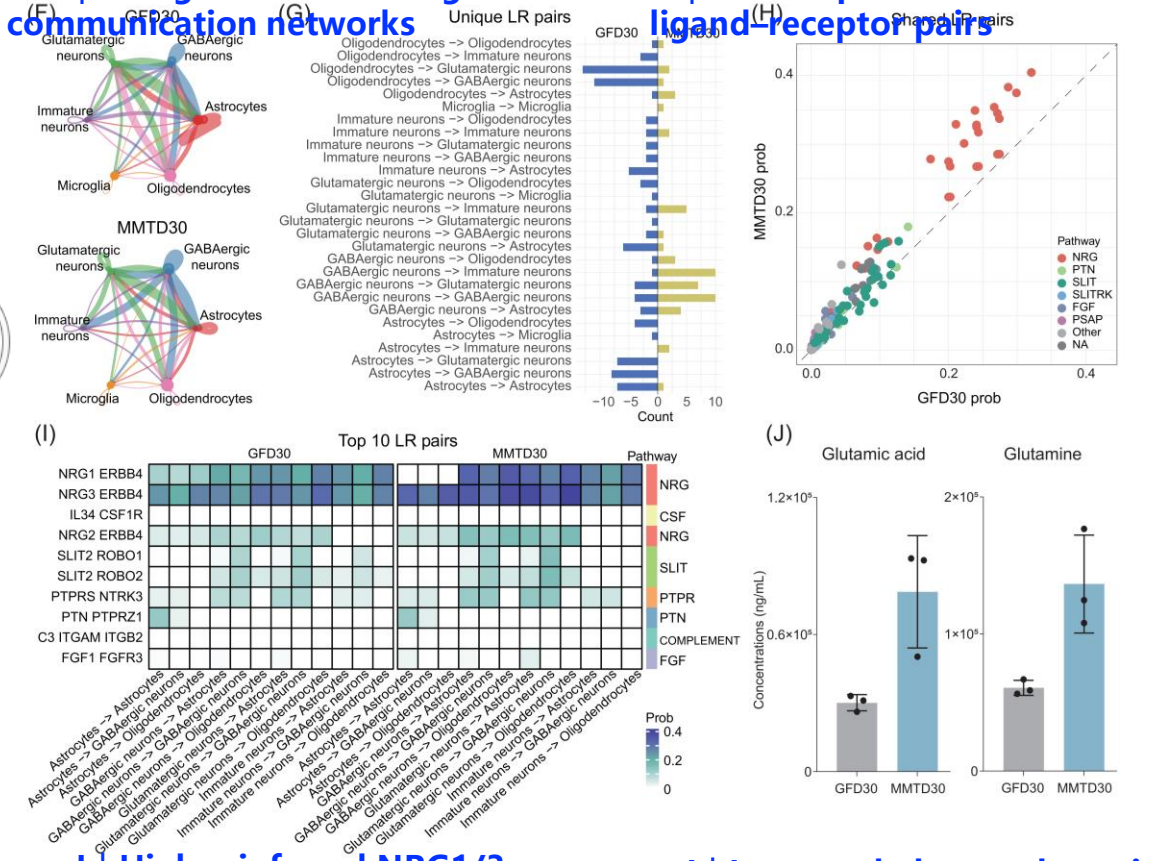
B | Three gene-expression patterns

C | Glutamatergic, GABAergic and immature neurons

F–G | Reorganized neuron–glia communication networks

H | Altered probabilities for shared ligand–receptor pairs





D | Differences in inferred neuronal trajectories

E | Region-specific neuronal subtype transcription

I | Higher inferred NRG1/3–ERBB4 communication

J | Increased plasma glutamic acid and glutamine

Figure 2. Maternal microbiota-associated remodeling of neuronal transcriptional states, developmental trajectories, intercellular communication, and plasma glutamate–glutamine metabolism.

Result 3 | Glial transcriptional states and regulatory networks

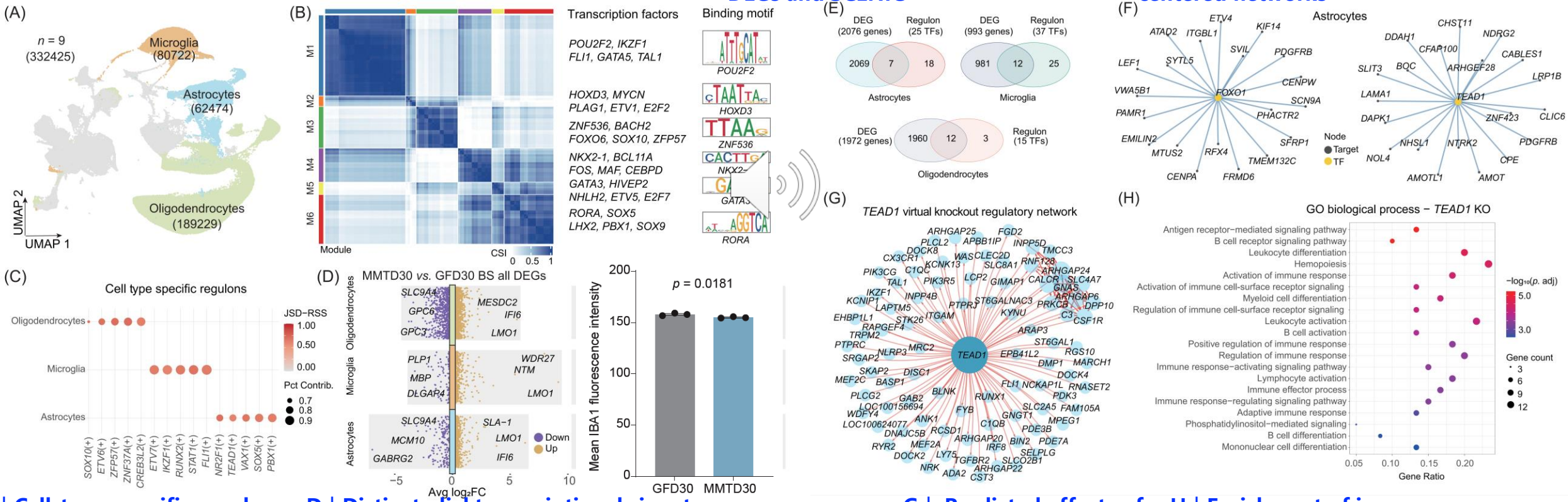
Oligodendrocytes, microglia and astrocytes showed cell-type- and region-specific transcriptional and regulatory responses, with substantial astrocytic heterogeneity. Integrated DEG–SCENIC analysis nominated TEAD1 as a candidate regulator; its virtual knockout predicted enrichment of immune-related processes.

A | Three major glial lineages

B | Six co-regulatory modules

E | Candidate regulators from DEGs and SCENIC

F | Predicted TEAD1- and FOXO1-centered networks



C | Cell-type-specific regulons

D | Distinct glial transcriptional signatures
Immunofluorescence validation of the microglial marker IBA1 in the hypothalamus

G | Predicted effects of virtual TEAD1 knockout

H | Enrichment of immune-related processes

Figure 3. Transcriptional regulatory programs and candidate regulons in major glial populations of the porcine brain.

Result 4 | HPA-axis and neuroendocrine regulation

Maternal microbiota transplantation was associated with altered HPA-axis cellular communication and stress-related transcriptional programs. Shared DEGs in the hypothalamus, pituitary and adrenal gland involved cellular and endoplasmic reticulum stress. MMTD30 piglets had lower plasma cortisol and higher serum IL-6, IL-1ra, IL-10 and TNF-α.

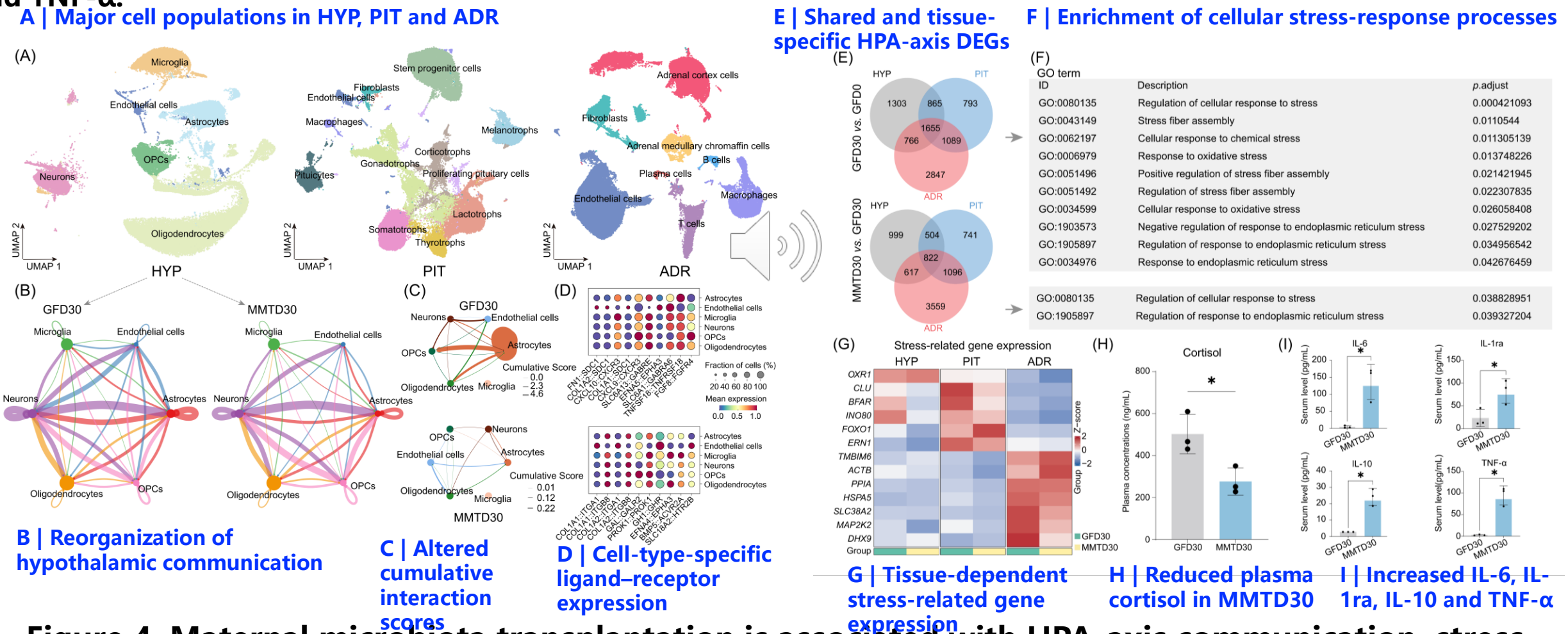
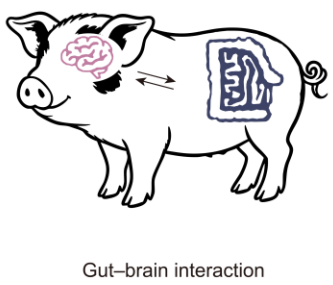


Figure 4. Maternal microbiota transplantation is associated with HPA-axis communication, stress-related transcriptional remodeling, and peripheral immune alterations.

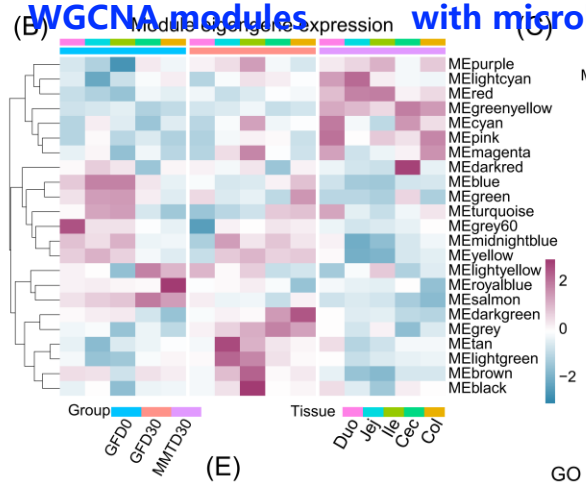
Result 5 | Intestinal transcriptomics and metabolomics

Maternal microbiota transplantation was associated with intestinal segment-specific transcriptional and metabolic remodeling. Transcriptional responses were more extensive in the small intestine, whereas 50 genes were consistently upregulated across all five segments. Intestinal metabolomics revealed segment-specific metabolic changes, while plasma metabolomics identified alterations in tryptophan- and indole-related metabolites.

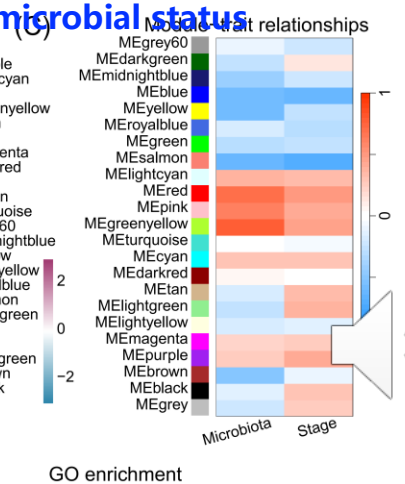
A | Intestinal arm of the gut–brain axis



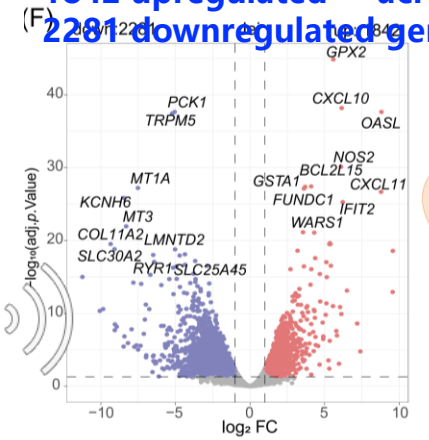
B | Segment-specific WGCNA modules



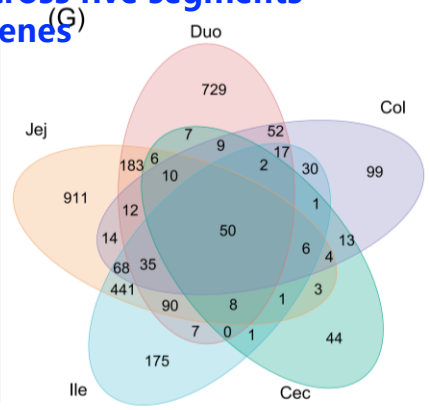
C | WGCNA modules associated with microbial status



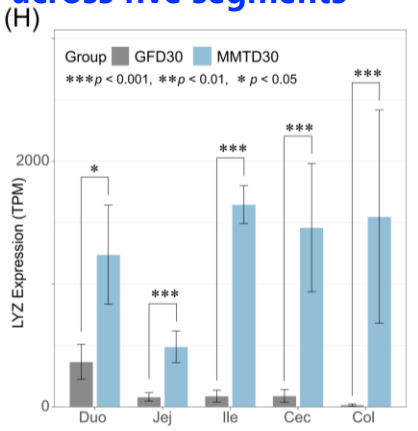
F | Jejunum: 1842 upregulated 2281 downregulated genes



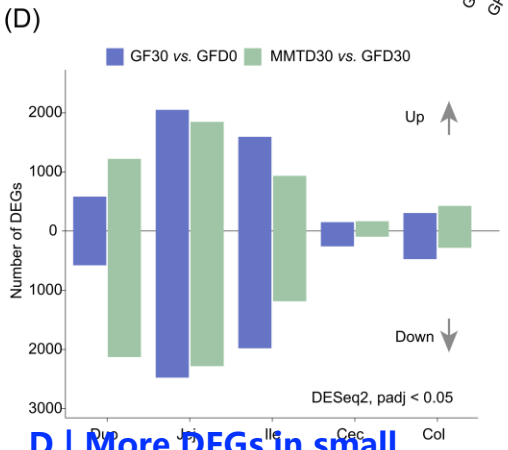
G | Fifty genes upregulated across five segments



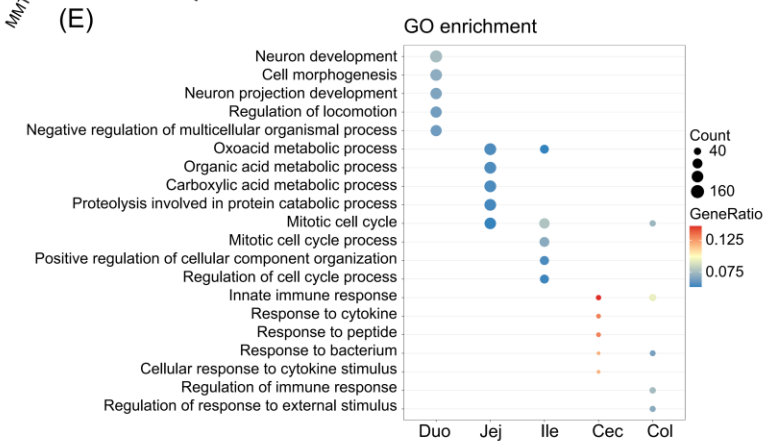
H | Higher LYZ expression across five segments



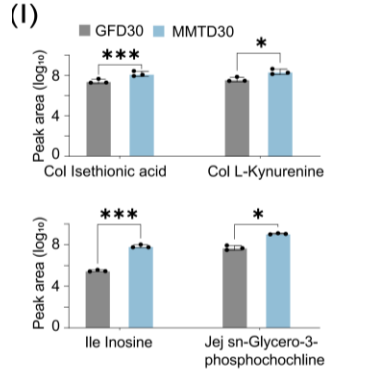
D | More DEGs in small than large intestine



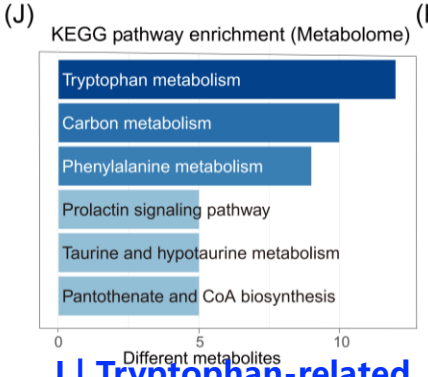
E | Segment-specific functional enrichment



I | Segment-specific metabolite changes



J | Tryptophan-related plasma pathway enrichment



K | Higher abundance of selected indole-related plasma metabolites

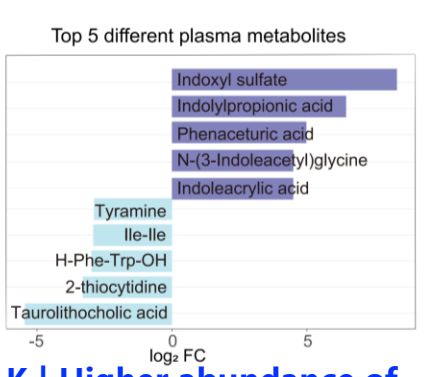
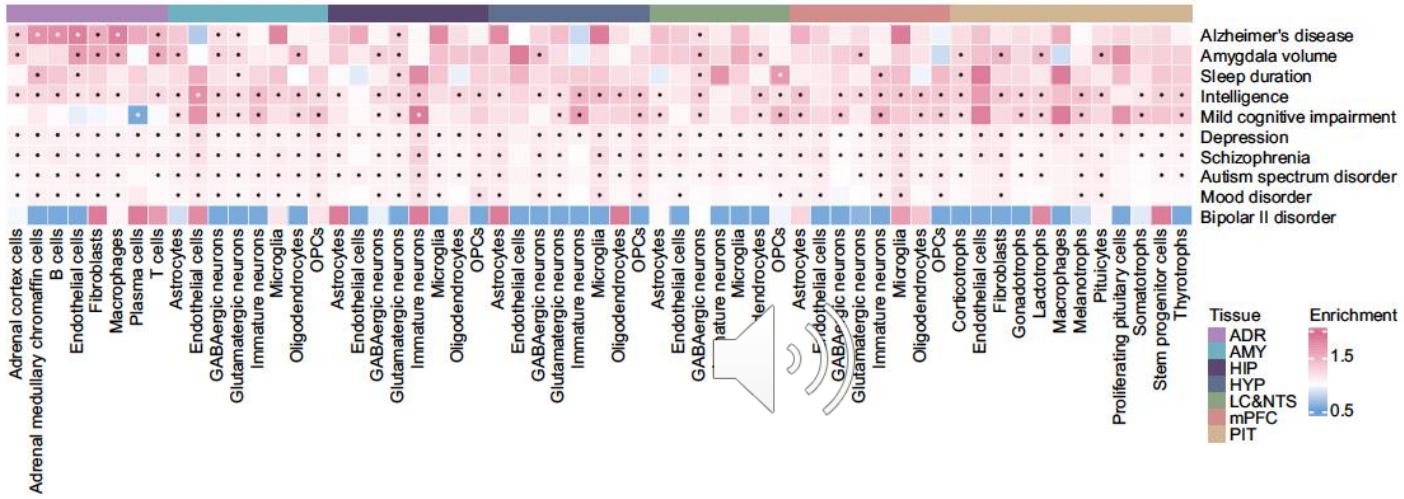


Figure 5. Maternal microbiota-associated intestinal transcriptional and metabolic remodeling along the gut–brain axis.

Result 6 | Cross-species genetic enrichment

S-LDSC identified cell-type-specific enrichment of human cognitive, neuropsychiatric, neuroanatomical, sleep-related and neurodegenerative trait-associated signals in microbiota-responsive porcine cells. gsMap further localized educational attainment and intelligence quotient-associated signals to selected hypothalamic cellular domains.

(A) **A | Cell-type-specific enrichment of human complex traits**



(B) **B | Spatial enrichment of EA2- and IQ-associated signals in HYP**

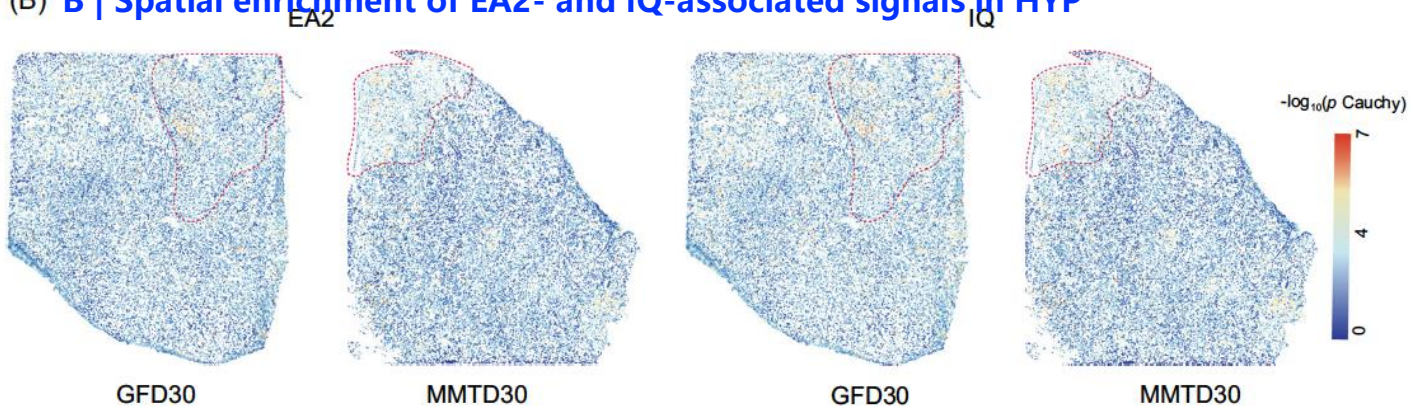


Figure 6. Cross-species genetic enrichment and spatial distribution of human complex-trait-associated signals across the porcine brain and HPA axis.

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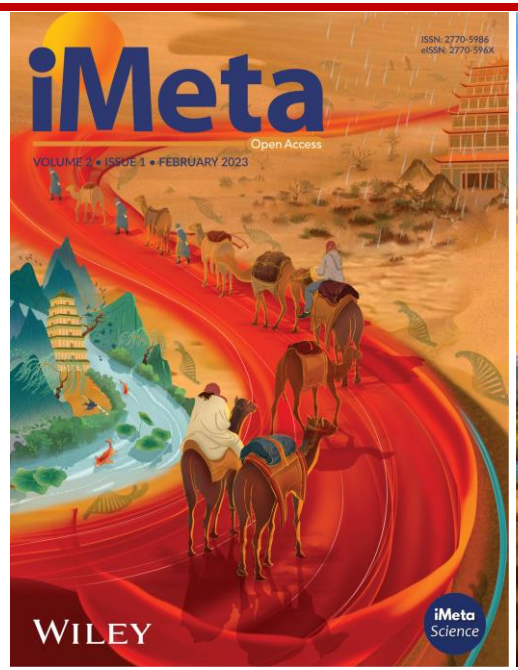

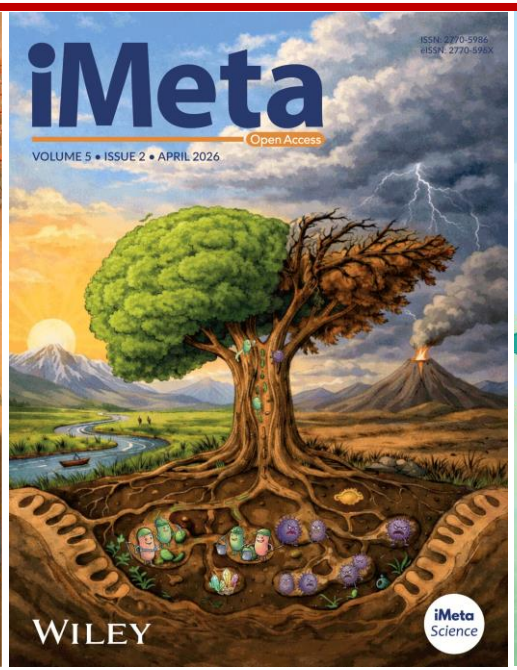

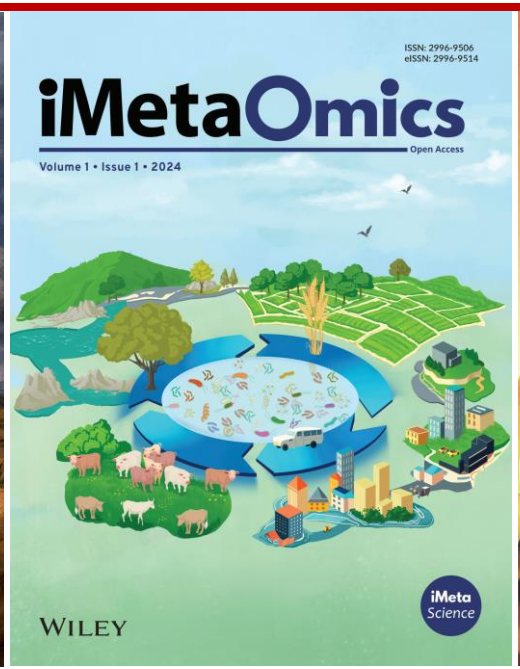

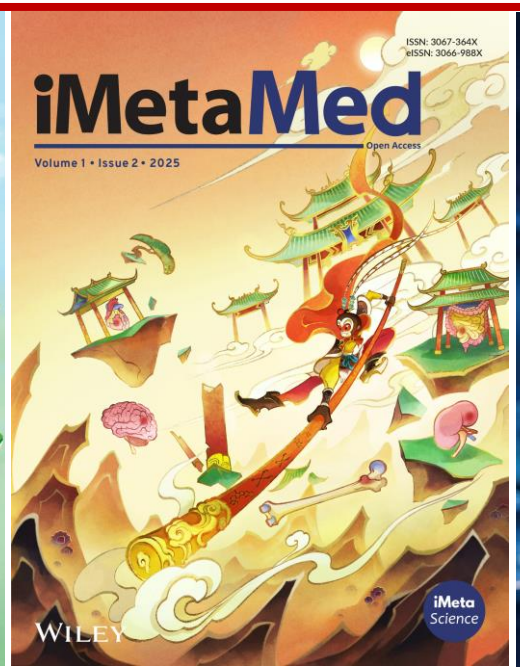

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